



PATENT
Attorney Docket No. EURA-004/00US
(Formerly 451194-101)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gopi M. Venkatesh et al.

Application No.: 10/713,929

Confirmation No.: 4820

Filed: November 14, 2003

Group Art Unit: 1615

For: MODIFIED RELEASE DOSAGE FORMS OF
SKELETAL MUSCLE RELAXANTS

Examiner: BARHAM, Bethany P.

DECLARATION UNDER 37 C.F.R. § 1.131

We, Dr. Gopi Venkatesh and James M. Clevenger declare as follows:

1. We are the named inventors of the above-noted application (Ser. No. 10/713,929)
2. We have read and understood the Official Action of January 11, 2008, and in particular the rejection of the pending claims under 35 U.S.C. §103 over the combination of U.S. Publ. No. 2004/0197407 (the '407 application) and U.S. Publ. Nos. 2003/0215496 or 2003/0099711.
3. We understand that the earliest asserted priority date of the '407 application is February 11, 2003, through the priority claim to U.S. Provisional Application Ser. No. 60/446,425.
4. The subject matter of the pending claims of the present application was invented by Gopi Venkatesh and James M. Clevenger (the named inventors) prior to February 11, 2003.
5. Example 3 of the instant application describes the formulation and production of a multiparticulate dosage form of cyclobenzaprine, wherein the cyclobenzaprine is coated on sugar spheres and covered with a water insoluble polymer to produced extended release beads (see paragraph 0045). Figure 4 of the instant application shows the release rate of the finished beads of Example 3 (e.g., Batch 805-AAA-105).

6. Exhibit A, dated before February 11, 2003, shows a "Master Formula" sheet documenting the production of the intermediate cyclobenzaprine coated beads used to make **Batch 805-AAA-105**. This intermediate batch (designated **Lot No. 837-AG-034**) comprises:

- "Sugar Spheres" (5475 g) coated with "cyclobenzaprine HCl" (1875 g) from "Acetone, NF 50/50% Ratio" and "USP Purified Water, 50/50% Ratio";
- seal coated with "2.00"% of "Opadry Clear YS-1-7006".

Exhibit B, dated before February 11, 2003, shows a "Master Formula" sheet documenting the actual production of **Batch 805-AAA-105** by coating the intermediate cyclobenzaprine beads of **Lot No. 837-AG-034** with an extended release water insoluble polymer:

- ER coating of **Lot No. 837-AG-034** with "Ethylcellulose 10P Premium (10 cps)" (363.6 g) and "Diethyl Phthalate" (36.4 g) dissolved in "Acetone, NF (98 parts)" and "USP Purified Water (2 parts)". Samples were collected with a coating weight of "10%" (designated **Batch or Lot No. 805-AAA-105**).

Exhibit C, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for "Lot # 805-AAA-105-10" (i.e., 10 wt.% ER coating, **Batch 805-AAA-105**). The data are identical to that presented in graphical form for the sample designated "10% ER Coating Wt., **Batch 805AAA105**" in Figure 4 of the instant application and shows that the 10% ER coated beads exhibit a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

7. Exhibit D, dated before February 11, 2003, is a batch record showing the ingredients of "Cyclobenzaprine HCl ER Beads", **Lot No. PE271EA001**:

- "Cyclobenzaprine HCl Intermediate Beads", Item code **PE249**; coated with "Ethylcellulose" and "Diethyl Phthalate".

Exhibit E, dated before February 11, 2003, documents the manufacture of "Cyclobenzaprine HCl MR Capsules, 30 mg", Lot No. **PF306EA001**:

- "White, Opaque Hard Gelatin Capsules, Size 4", filled with "Cyclobenzaprine HCl Extended Release Beads", Item code **PE271**.

Exhibit F, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for clinical batch "Lot # PF306EA001". The data are identical to that presented in graphical form for the clinical sample designated "PF306EA001" in Figure 6, Examples 4 and 5 of the instant application. Formulation PF306EA001 shows a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

8. Thus, Exhibits A and B document the production of the identical multi-particulate cyclobenzaprine dosage forms described in Example 3 of the present application, and as set forth in the instant claims, before February 11, 2003.

9. Thus, Exhibits D and E document the production of the identical clinical batch described in Examples 4 and 5 of the present application, and as set forth in the instant claims, before February 11, 2003.

10. We further declare that all statements made herein on our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Respectfully submitted,

G. M. Venkatesh

Gopi Venkatesh

2/13/2008

Date

James M. Clevenger

James M. Clevenger

2/13/2008

Date

Exhibit A

Master Formula

Page 1 of 1

Product Name: Cyclobenzaprine HCl, Drug Layered Beads Batch Number: 837A0694 Date:

Physical Description: Off White Capsule Size: N/A Batch Size: 7500.0 gms

Imprint (Upper): N/A Imprint (Lower): N/A Label (mg / Unit): N/A Unit Weight (mg): N/A

Written By: A.Gallo *A. Gallo* Reviewed By: Room #: 1472 Temperature: 6.0 °C Humidity: 72.0 % Time: 7:50 AM

ITEM #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity	Quantity	Quantity	Quantity	Weighted	Checked	Date
			Mg / Unit	Gm / batch	Weighted	By	By		
1	*Cyclobenzaprine HCl	C14607401	25.00	1875.0 gm	1875.0	AK			
2	Sugar Spheres 20 - 25 Mesh (Hansen)	RD - 991114	73.00	5475.0 gm	5475.0	AK			
3	**Opadry Clear YS - 1 - 7006	H10507376	2.00	150.0 gm	150.0	AK			
4									
5									
6									
7									
8									
9									
10	Acetone, NF 50/50 % Ratio	A10707332		2812.50 ml	2812.50	AK			
11	USP Purified Water, 50/50 % Ratio	W-10002061B		2812.50 ml	2812.50	AK			
12	USP Purified Water @ 10.0 % of Seal Coat	W-10002061B		1350.0 ml	1350.0	AK			
Total:			100.00	7500.0 gm	7500.0	AK			

Objective: to evaluate dose @ 25.0 % Using GPCG S

Note: Acetone, NF / USP Purified Water 50/50 Ratio.

* Item #10,11, 12 is used to make coating solutions. Both mg unit and g batch units do not reflect entire.

Exhibit B

Project No. _____

TITLE CYCLOBENZAPRINE HCl EC BEADSBook No. 805From Page No. 104

Purpose: To EC coat Cyclobenzaprine HCl drug layered beads using solvent (50:50) Acetone : H₂O as a medium. The drug layered beads were then Ethyl Cellulose coated using Acetone : H₂O (98:2). The EC was done using Glue GPC-5 Wurster.

Master Formula

Page 1 of 1

Product Name: Cyclobenzaprine HCl - Extended Release Beads (25.0 mg)									
Physical Description : Extended Release Coating									
Lot # 885-AAA-105									
Date : _____									
Item #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity % Wt W	Quantity Mg / Unit	Quantity Cost Batch	Quantity Weighted	Weighted By	Checked By	
1.	Cyclobenzaprine HCl, Drug Layered Beads	837-AG-034	3600.0			3600.0	AAA		
2.	Ethylcellulose 10P Premium (10cps), NF	B11407226	363.6			364.0	AAA		
3.	Diethyl Phthalate, USP	D11807500	36.4			36.4	AAA		
10.	Acetone, NF (98 parts)	A10707332	5639.0			5639.0	AAA		
11.	Purified Water, USP (2 parts)	W100-01	115.0			115.0	AAA		
Total:									
Objective: Evaluating Dose @ 10.0 % Samples were taken @ 7, 8, 9, & 10% of EC applied.									

AAA

To Page No

Witnessed & Understood by me,

Date

Invented by

Anthony A. Agui

Date

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TITLE Cyberstalking Me

From Page No. 119

42117- [REDACTED]

For Septern Sect
See p. 614

Stability Conditions		Reference		Std 2 Criteria (mg)		Std 3 Conc. (mg/ml)		Actual Assay		Avg. (%) Release		σ _{rel}		(%) RSD		Spec.		Pass/Fail	
Vessel Weight (mg)		Active Vial (mg)																	
1	140.85	31.15																	
2	141.89	31.35																	
3	142.03	31.38																	
4	139.28	30.78																	
5	141.04	31.17																	
6	140.07	30.98																	
Info	Area	Std Avg.	(%) Released	Avg. (%) Release	σ _{rel}	(%) RSD	Spec.	Pass/Fail											
Std 1	625879																		
1.1	30087		8	8	0.5	0.1	FID	PO											
1.2	37241		8																
1.3	31848		5																
1.4	31505		5																
1.5	34893		8																
1.6	33750	(Std 182)	8																
Std 2	524333	634100																	
2.1	140530		25	26	1.0	4.2	NMT 60%	FAIL											
2.2	191088		28																
2.3	136303		23																
2.4	135882		23																
2.5	146973		25																
2.6	148717	(Std 263)	28																
Std 3	525852	525883																	
3.1	291002		49	48	1.3	2.8	30% - 80%	FAIL											
3.2	283066		48																
3.3	277113		48																
3.4	274032		47																
3.5	283105		49																
3.6	287012	(Std 544)	49																
Std 4	634819	634726																	
4.1	383336		81	80	1.4	2.3	FID	PO											
4.2	364024		80																
4.3	357439		56																
4.4	340631		58																
4.5	364481		61																
4.6	356000	(Std 445)	80																
Std 5	629639	520679																	
5.1	408548		68	67	1.5	2.3	80% - 90%	FAIL											
5.2	410530		66																
5.3	395003		63																
5.4	367481		65																
5.5	408778		68																
5.6	403770	(Std 546)	68																
Std 6	628966	627992																	
6.1	498086		78	77	1.2	1.8	FID	PO											
6.2	483716		77																
6.3	456263		78																
6.4	446242		76																
6.5	468754		76																
6.6	458622	(Std 647)	77																
Std 7	625880	626098																	
7.1	604593		84	83	1.8	1.2	N.Y. 75%	FAIL											
7.2	604335		94																
7.3	491852		63																
7.4	483636		62																
7.5	501854		84																
7.6	601349	(Std 748)	84																
Std 8	626741	626211																	

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$$\text{Revised} = \frac{(50349)}{14.6} \div 536211 \quad (0.09013 \text{ mm}) \quad (900 \text{ mL}) \quad (100\%)$$

$$\quad \quad \quad (140.07 \text{ mm}) \quad (22.1\% / 100\%)$$

1.78	1.78
1.78	1.78

Chromatoporus *Stuedi* in Box 891

To Page No. 23

Witnessed & Understood by me,
Dan Hendley

Date _____

Invented by _____

Recorded by *Y. H. H. H. H.*

Date _____

ISSUED BY Q.A.

Kurand America, Inc.
Cyclobenzaprine HCl ER Beads
Batch Size: 85 kg (Theoretical)
MF #: A-59PE271-A

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Lot #: PE271EA001	Date of Manufacturing: [REDACTED]
Effective Date: [REDACTED]	
Prepared By: [Signature]	Date: [REDACTED]
Mfg. Approval By: [Signature]	Date: [REDACTED]
R&D Approval By: Phil Perel	Date: [REDACTED]
QA Approval By: [Signature]	Date: [REDACTED]
QA Issue: [Signature]	Date: [REDACTED]
QA Audited By: [Signature]	Date: [REDACTED]

Item No.	Item Code	Bead Dosage (mg/g)	% per Batch (w/w)	Ingredient Name	Theoretical Quantity Per Batch**
1	PE249	910.00	91.00	Cyclobenzaprine HCl Intermediate Beads	77.4 Kg
2	E114	81.25	8.13	Ethylcellulose, Premium Std 10cps	6.9 Kg
3	D118	8.75	0.88	Diethyl Phthalate, NF	0.75 Kg
4	A107 -	—	—	Acetone, NF*	116.7 Kg
5	W100	—	—	Purified Water, USP*	2.4 Kg
		1000.00	100.01	TOTAL=	85.0 Kg

*Removed from process during the drying process

**Actual batch is based on the actual quantity of the Intermediate Beads available for use. See page 2

Exhibit D

ISSUED BY Q.A.

Eurand America, Inc.
Cyclobenzaprine HCl MR Capsules, 30 mg
Batch Size - 130,000 Capsules (Theoretical))
MF#: A-60PF306-A

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Lot # PF306EA		001		Date of Manufacturing:	
Effective Date:		[REDACTED]			
Prepared By: <i>James M. Elmer</i>		Date: [REDACTED]			
MFG. Approval By: <i>J. D. [REDACTED]</i>		Date: [REDACTED]			
R&D Approval By: <i>L. M. Venkatesh</i>		Date: [REDACTED]			
QA Approval By: <i>Thomas M. Purdie</i>		Date: [REDACTED]			
QA Issue: <i>Thomas M. Purdie</i>		Date: [REDACTED]			
QA Audited By: <i>Thomas M. Purdie</i>		Date: [REDACTED]			

Item Code	Item No.	mg per capsule	% per Capsule (w/w)	Ingredient Name	Quantity per Batch
G134	1	37.00 ¹	21.91	White, Opaque Hard Gelatin Capsules, Size 4,	4.81 kg
PE271	2	131.87 ²	78.09	Cyclobenzaprine HCl Extended Release Beads	17.14kg
Total		168.87			21.95 kg

¹Based on a theoretical empty capsule weight of 37.0 mg
²Equivalent to 30 mg of Cyclobenzaprine Hydrochloride (Beads based on a theoretical assay of 22.75%)

Exhibit E

Exhibit F

Cyclobenzaprine 30mg MR Capsules Lot# PF306EA001

1 hour				Avg. STD	8 hour				Avg. STD
CHKSTD	282100	CHKSTD	258778	259438	CHKSTD	283383	CHKSTD	270750	287057
1	10845	7	14041		1	205885	7	220888	
2	5830	8	14418		2	215818	8	218838	
3	12708	9	0		3	218018	9	205783	
4	11845	18	14435		4	211804	10	219400	
8	11232	11	15263		5	220533	11	211189	
8	10480	12	13404		8	214893	12	222248	
CHKSTD	258775	CHKSTD	282386	289581	CHKSTD	270750	CHKSTD	283358	287053

2 hour				Avg. STD	12 hour				Avg. STD
CHKSTD	282388	CHKSTD	283589	282988	CHKSTD	283358	CHKSTD	281737	282547
1	73230	7	83090		1	232004	7	247858	
2	80480	8	88178		2	245230	8	245587	
3	80522	9	81274		3	248103	9	230755	
4	77577	10	84348		4	245048	10	248980	
5	81204	11	78231		5	281589	11	237970	
8	80205	12	85540		8	244480	12	282555	
CHKSTD	283589	CHKSTD	282191	282890	CHKSTD	281737	CHKSTD	281580	281884

4 hour				Avg. STD	18 hour				Avg. STD
CHKSTD	282191	CHKSTD	281515	281853	CHKSTD	281590	CHKSTD	281252	281421
1	138063	7	189208		1	247344	7	284018	
2	143494	8	158284		2	282134	8	282718	
3	145158	9	151818		3	283883	9	242844	
4	143021	10	159810		4	288831	10	285913	
8	149228	11	149087		5	288488	11	284822	
8	145149	12	180801		8	285058	12	289882	
CHKSTD	281515	CHKSTD	288598	286057	CHKSTD	281252	CHKSTD	282478	281884

8 hour				Avg. STD		STD conc 0.03007 mg/ml		Strength 30 mg		
CHKSTD	288598	CHKSTD	288252	287425						
1	182178	7	197178							
2	191272	8	194580							
3	192435	9	188135							
4	187985	10	187029							
8	198802	11	188727							
8	190502	12	198823							
CHKSTD	288252	CHKSTD	283383	284808						

1 hour (FIO)				Average: 4 %	8 hour (99-99%)				Average: 73 % Pass
1	4	7	5		1	69	7	78	
2	2	8	5		2	73	8	74	
3	4	9	0		3	73	9	70	
4	4	10	5		4	72	10	74	
5	4	11	5		5	74	11	71	
8	4	12	5		8	73	12	75	

2 hour (0-49%)				Average: 28 % Pass	12 hour (FIO)				Average: 84 %
1	25	7	29		1	80	7	85	
2	28	8	30		2	84	8	85	
3	28	9	28		3	85	9	80	
4	27	10	29		4	84	10	88	
8	28	11	27		5	88	11	82	
8	28	12	29		8	84	12	87	

4 hour (38-89%)				Average: 51 % Pass	18 hour (88.7-78%)				Average: 90 % Pass
1	47	7	64		1	85	7	91	
2	49	8	64		2	90	8	91	
3	50	9	52		3	91	9	84	
4	49	10	64		4	89	10	92	
5	51	11	51		5	93	11	88	
8	50	12	58		8	91	12	93	

8 hour (FIO)				Average: 85 %
1	61	7	67	
2	65	8	68	
3	65	9	63	
4	63	10	67	
5	67	11	64	
8	64	12	68	